REMARKS

Claims 51 and 59-63 have been cancelled. The amendment to claim 52 is supported by claims 62 and 63. New claims 73-78 are supported by claims 64, 65 and 68-71, respectively. No new matter has been added. Upon entry of this amendment, claims 52-58 and 64-78 are present, with claims 52, 53, 55, 57, 58, 64-71 and 73-78 active.

Applicants thank Examiner Gangle for the courteous and helpful discussion held with applicants' representative. During the discussion, it was indicated that incorporating claims 62 and 63 into claim 52, while addressing the issues under 35 U.S.C. 112, second paragraph, would advance the application. Applicants also thank Examiner Gangle for withdrawal of the prior objections, and the prior rejection of the claims under 35 U.S.C. 102.

The claimed invention provides a composition for delivery of a therapeutic agent to a neuronal cell, comprising the therapeutic agent, a neuronal cell targeting component, and a translocation domain (page 3, line 36 to page 5, line 7 of the present application). The therapeutic agent is an ADP-ribosyltransferase. The neuronal cell targeting component comprises a Hc domain of botulinum C1 toxin, or a fragment thereof which retains the function of the native Hc domain.

The rejection of claims 52, 53, 55, 57, 58, 60, 61 and 64-71 under 35 U.S.C. 103, over Shone et al. in view of Lehmann et al., has been obviated by appropriate amendment. Claims 62 and 63 have been incorporated into claim 52. Withdrawal of this ground of rejection is respectfully requested.

The rejection of the claims under 35 U.S.C. 103, over Shone et al. in view of McKerracher et al., is respectfully traversed. McKerracher et al. teaches against the use of receptor-mediated targeting mechanisms, such as a neuronal cell targeting component.

Shone et al. describes a composition for the delivery of superoxide dismutase to neuronal cells. The composition includes a superoxide dismutase (SOD) linked to a neuronal targeting component, which component includes a first domain that binds to a neuronal cell and a second domain that translocates the SOD into the neuronal cell

(abstract). The linker is cleavable and thus, in use, after translocation of the SOD into the cell, the linker is cleaved to release SOD from the neuronal cell targeting domain (page 5, last paragraph). Shone et al. does not suggest a composition comprising an ADP-ribosyl transferase.

McKerracher et al. describes ADP-ribosyl transferase fusion proteins. The conjugate includes a transport subdomain in addition to an active agent moiety (col. 4, lines 33-45). Noted in this reference is that other methods of delivery of C3 (an ADP-ribosyl transferase) which use a receptor-mediated targeting mechanism, have the disadvantage that much of the C3 in the cell will be restrained within a membrane compartment (col. 4, lines 16-30). The reference expands on the disadvantages of using a receptor-mediated targeting mechanism:

> Several receptor-mediated transport strategies have been used to try and improve function of ADP ribosylases: these methods include fusing C2 and C3 sequences and use of receptor-mediated transport with the diphtheria toxin receptor. These methods have not been demonstrated to dramatically increase the potency of C3. Moreover, these proteins require receptor-mediated transport. This means that the cells must express the receptor, and must express sufficient quantities of the receptor to significantly improve transport. Moreover, when C3 enters the cell by endocytosis, it will be locked within a membrane compartment, and therefore most of it will not be available to inactivate Rho. In the case of diphtheria toxin, not all cells express the appropriate receptor, limiting its potential use. The clinical importance for any of these has not been tested or shown.

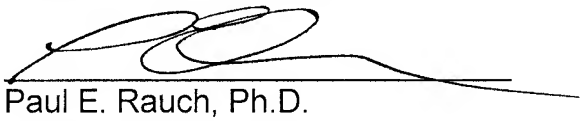
(col. 30, line 64, to col. 31, line 14; citations omitted). Accordingly, McKerracher et al. teaches against the use receptor-mediated targeting mechanisms.

The claimed invention provides a composition including an ADP-ribosyl transferase and a neuronal cell targeting component. Shone et al. describes a composition for the delivery of superoxide dismutase to neuronal cells, but does not suggest a composition containing an ADP-ribosyl transferase. Although McKerracher et al. describes ADP-ribosyl transferase fusion proteins, this reference teaches away from using receptor-mediated targeting mechanisms, such as a neuronal cell targeting component. Accordingly, the claimed invention is not obvious over the cited references. Withdrawal of this ground of rejection is respectfully requested.

The rejection of claims 62 and 63 (now incorporated into claim 52) has been obviated by appropriate amendment. Applicants note that "C3Stau2", "C3Stau1" and "C3bot" are terms of art, as described in Pautsch et al. (the EMBO Journal (2005) **24**, 3670-3680; cited in the attached information disclosure statement). These terms have been replaced with more explanatory language. Withdrawal of this ground of rejection is respectfully requested.

Applicants submit that the present application is now in condition for allowance. Early notice of such action is respectfully requested.

Respectfully submitted,



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